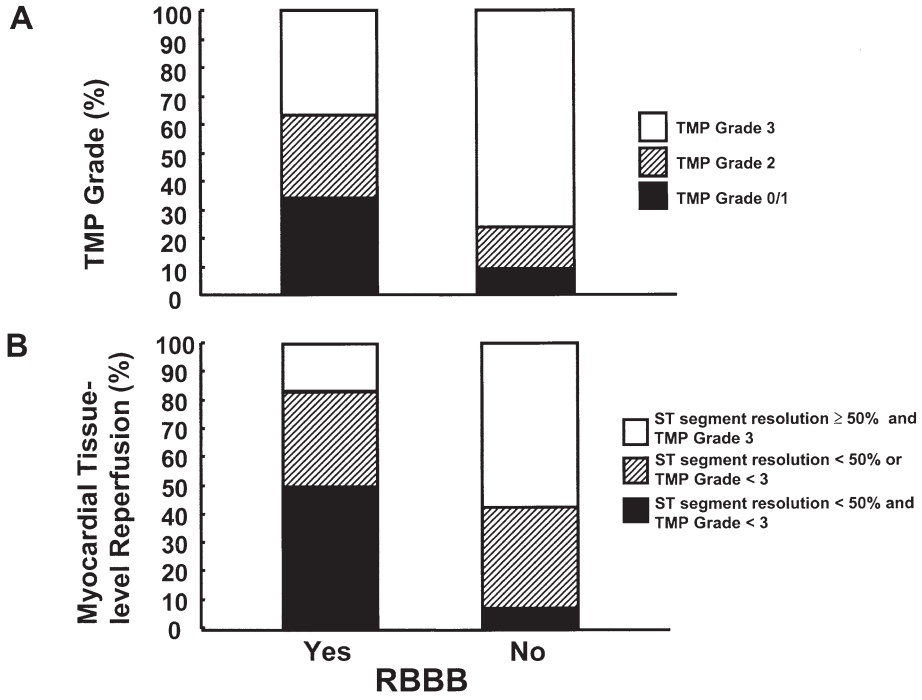

Figure 1. **(A)** Thrombolysis In Myocardial Infarction myocardial perfusion (TMP) grade by the presence or absence of right bundle branch block (RBBB) in 105 patients with ST-segment elevation myocardial infarction (STEMI). **(B)** Myocardial tissue-level reperfusion by the presence or absence of RBBB in 105 patients with STEMI.

***Makoto Suzuki, MD**

*Division of Cardiology
Ehime Prefectural Central Hospital
83 Kasuga, Matsuyama
Ehime 790-0024
Japan
E-mail: suzuki-m@mail.netwave.or.jp

Tomoki Sakaue, MD
Masamichi Tanaka, MD
Eiki Hirose, MD
Hideyuki Saeki, MD
Tsuyoshi Matsunaka, MD
Shinichi Hiramatsu, MD
Yukio Kazatani, MD

doi:10.1016/j.jacc.2006.02.034

REFERENCES

1. Melgarejo-Moreno A, Galcera-Tomas J, Garcia-Alberola A, et al. Incidence, clinical characteristics, and prognostic significance of right bundle-branch block in acute myocardial infarction. A study in the thrombolytic era. Circulation 1997;96:1139–44.
2. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-executive summary. Circulation 2004; 110:588–636.
3. Roe MT, Ohman EM, Maas AC, et al. Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. J Am Coll Cardiol 2001;37:9–18.
4. Poli A, Fetiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty. Real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. Circulation 2002;106:313–8.
5. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125–30.
6. Schroder R, Dissmann R, Bruggemann T, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994;24:384–91.
7. Ricou F, Nicod P, Elizabeth G, Henning H, Ross J Jr. Influence of right bundle branch block on short- and long-term survival after acute myocardial infarction. J Am Coll Cardiol 1991;17:858–63.
8. Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation 2002;105:656–62.

Serum Adiponectin Levels Are an Independent Predictor of the Extent of Coronary Artery Disease in Men

To the Editor: Several risk factors for the development of coronary artery disease (CAD) have been identified, correlating with the incidence and progression of atherosclerotic disease. Low adiponectin, an adipocytokine, appears to be a clinically important mediator of atherosclerosis. Thus, prospective studies have shown that elevated adiponectin levels predicted a decreased risk of myocardial infarction in the general population and among patients with type 2 diabetes (T2D) (1,2). No study to date has combined serum adiponectin levels and polymorphisms with an influence on adiponectin levels to investigate the potential association of adiponectin with the extent of coronary atherosclerosis as measured by several defined angiographic scores. We therefore investigated the relation of serum adiponectin to the extent of CAD with the help of two established scores: "severity score" (SS) and "extent score" (ES) (3,4).

Two hundred forty-seven individuals, ages 31 to 83 years, who were undergoing clinically indicated coronary angiography at the University Hospital Heidelberg were enrolled. Treatment with peroxisome proliferator-activated receptor (PPAR)-alpha or PPAR-gamma agonists, known to affect adiponectin levels, was an exclusion criterion. Serum samples were obtained before angiography and frozen at −70°C until analyses were performed. Serum adiponectin was determined by enzyme-linked immunosorbent assay (B-Bridge-International, San Jose, California). The extent of angiographically documented CAD was quantified by two independent investigators as follows: 1) the SS as one-vessel, two-vessel, or three-vessel disease, defined as stenosis of more than 50% of the luminal diameter (3); and 2) the ES, in which atherosclerotic wall irregularities in 10 defined segments of the coronary arteries were evaluated (4). Two-tailed bivariate correlations were determined by the Spearman correlation coefficient, and comparisons between two sets of patients were performed with the Mann-Whitney *U* test. Comparisons between quartiles (SS) and quintiles (ES) were performed with the Kruskal-Wallis test. The study was approved by the ethics committee of Heidelberg University. All patients gave written informed consent.

Coronary artery disease was found in 172 patients. Compared with the 75 patients without CAD, the 172 men with CAD were older, more likely to be a current smoker, and had higher blood pressure and lower high-density lipoprotein cholesterol (data not shown). Adiponectin levels were significantly lower in patients with CAD than in those without (4.8 vs. 7.5 μg/ml; $p < 0.001$). The severity of CAD as quantified by SS correlated significantly with serum adiponectin ($p < 0.001$ by Kruskal-Wallis test) (Fig. 1A). In addition to severity of CAD, we further found a significant inverse correlation between serum adiponectin and the more sensitive ES ($r = -0.23$; $p < 0.001$). When patients were divided into quintiles of increasing ES, a stepwise decrease in adiponectin levels was associated with increasing extent of atherosclerotic wall irregularities ($p < 0.001$ by Kruskal-Wallis test) (Fig. 1B).

Multivariate regression models were used to estimate the partial association between serum adiponectin and the extent of CAD. In the first model, adjusted for age and body mass index, adiponectin was a significant and independent predictor of both SS and ES (Table 1, Model 1). When traditional cardiovascular risk factors entered the regression analysis (Table 1, Model 2) and, finally, markers of systemic inflammation (Table 1, Model 3) were added, adiponectin remained an independent predictive factor for the extent of CAD in both scores. This result was unaffected by the current medication of the study population.

To investigate potential associations between genetic determinations of serum adiponectin and the extent of CAD, we further screened for two genetic variations known to influence adiponectin expression: a silent mutation in exon-2 of the adiponectin gene (T94G) (5) and a polymorphism in exon B of the PPAR-gamma-2 gene (Pro12Ala) associated with decreased serum adiponectin (6). The allele frequencies of the PPAR-gamma-2–Pro12Ala and adiponectin-T94G substitution were 0.214 and 0.173, respectively. Both polymorphisms were in genetic equilibrium according to the Hardy-Weinberg law, and the PPAR-gamma-2 polymorphism was not in linkage disequilibrium with the adiponectin polymorphism.

Serum adiponectin was lower among patients with PPAR-gamma-2–Pro12Ala (Ala-allele: 3.9 ± 0.4 μg/ml vs. Pro-allele: 5.9 ± 0.4 μg/ml; $p = 0.001$) and was increased in patients with adiponectin-T94G (G-allele: 7.6 ± 0.6 μg/ml vs. T-allele: 5.1 ± 0.5 μg/ml; $p < 0.001$). Moreover, patients with PPAR-gamma-2–Pro12Ala showed increased CAD in ES (Ala-allele: 34.4 ± 4.0 vs.

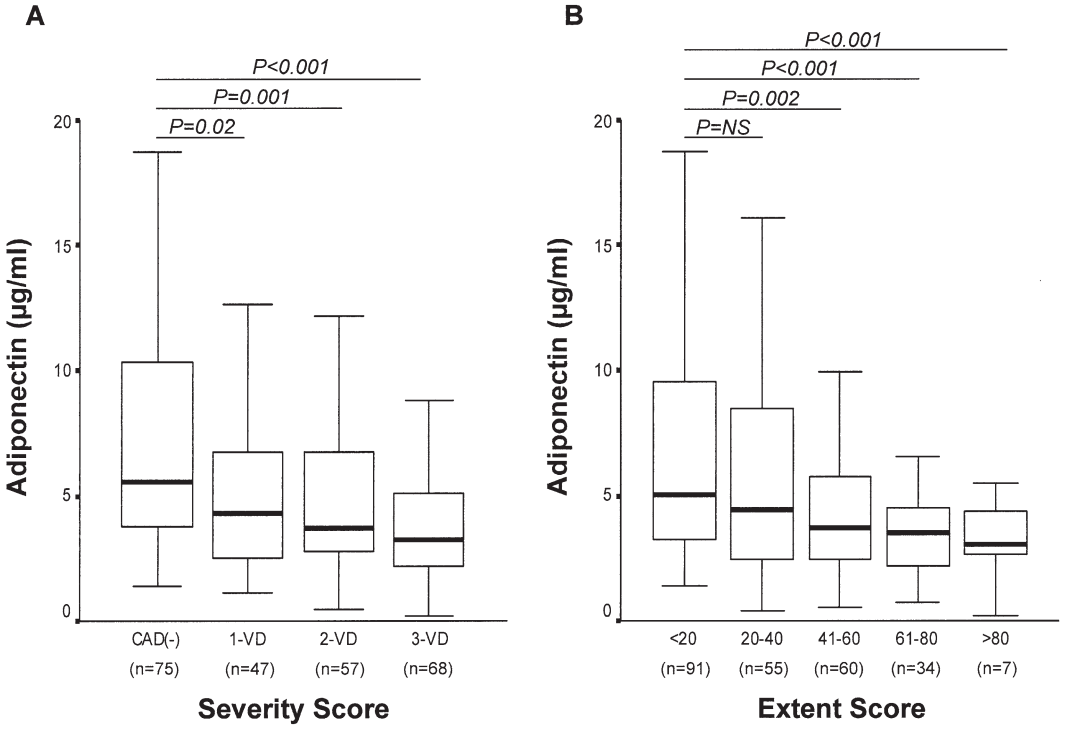

Figure 1. Associations between serum adiponectin levels and coronary artery disease (CAD) in men. The **central line** represents the median, the **boxes** span from the 25th to 75th percentiles, and the **error bars** extend from the 10th to 90th percentiles. **(A)** A stepwise decrease in adiponectin levels was associated with the number of >50% stenosed vessels (severity score). VD = vessel disease. **(B)** A stepwise decrease in adiponectin levels was associated with the extent of atherosclerotic wall irregularities (extent score).

JACC Vol. 47, No. 10, 2006
May 16, 2006:2118–29

Table 1. Multivariate Regression Models Predicting the Extent of Coronary Artery Disease

	Severity Score								Extent Score							
	Model 1			Model 2			Model 3			Model 1			Model 2			Model 3		
Variable	β	t	p Value	β	t	p Value	β	t	p Value	β	t	p Value	β	t	p Value	β	t	p Value
Adiponectin*	−0.27	−4.41	<0.001	−0.21	−3.17	<0.01	−0.15	−2.10	**0.037**	−0.29	−4.67	<0.001	−0.24	−3.54	<0.01	−0.17	−2.43	**0.016**
Age	0.26	4.36	<0.001	0.24	4.08	<0.001	0.27	4.25	0.001	0.24	3.92	<0.001	0.22	3.66	<0.01	0.25	3.87	**0.001**
BMI	0.10	1.67	NS	0.04	0.68	NS	0.11	1.63	0.105	0.06	1.01	NS	0.01	0.01	NS	0.05	0.73	0.468
LDL-C				0.16	2.60	<0.01	0.14	2.21	**0.028**				0.15	2.40	<0.05	0.13	2.01	**0.046**
HDL-C				−0.10	−1.55	NS	−0.14	−2.02	**0.045**				−0.07	−1.08	NS	−0.12	−1.69	0.092
Triglycerides*				−0.03	−0.40	NS	−0.04	−0.52	0.604				−0.03	−0.43	NS	−0.04	−0.53	0.599
Current smoker				0.20	3.38	<0.01	0.22	3.41	**0.001**				0.21	3.41	<0.01	0.26	3.94	**0.001**
Diabetes				0.02	0.40	NS	0.03	0.49	0.622				0.04	0.59	NS	0.05	0.81	0.418
Hypertension				0.14	2.38	<0.05	0.16	2.55	**0.011**				0.17	2.79	<0.01	0.19	3.06	**0.003**
hsCRP*							0.19	2.44	**0.015**							0.16	2.13	**0.035**
IL-6*							0.10	1.37	0.174							0.01	0.18	0.856
r			0.38			0.493			0.509			0.369			0.485			0.503
r^2			0.15			0.243			0.260			0.136			0.235			0.253

*Log-transformed variables; **Bold** indicates values of statistical significance ($p < 0.05$).
BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; IL = interleukin; LDL-C = low-density lipoprotein cholesterol.

Pro-allele: 26.0 ± 2.7; p = 0.03) and a tendency toward increased CAD in SS (Ala-allele: 1.60 ± 0.19 vs. Pro-allele: 1.34 ± 0.09; p = 0.09). Patients with the adiponectin-T94G variant had significantly less CAD in both angiographic scores: ES (G-allele: 21.9 ± 3.1 vs. T-allele: 30.7 ± 2.3; p = 0.03) and SS (G-allele: 1.02 ± 0.14 vs. T-allele: 1.53 ± 0.10; p = 0.01). In an additional linear regression analysis with SS or ES as dependent variable, only adiponectin remained a significant predictor of CAD, with the two polymorphisms being inter-correlated with adiponectin (data not shown).

In summary, these data demonstrate that serum adiponectin levels and the extent of CAD show a significant correlation in men. These results were obtained with two established scores of which the ES in particular has been demonstrated to better correlate with cardiovascular risk factors than other scores (4). Furthermore, we demonstrate that genetic variations known to affect adiponectin levels were significantly associated with the extent of CAD. This is in accordance with a recent study reporting a genetic variability of the adiponectin gene (G276T) to be associated with a reduced cardiovascular risk in patients with T2D (7). Our results indicate that the measurement of serum adiponectin might represent a novel diagnostic tool to stratify patients at risk for CAD and to identify those patients who would benefit most from preventive strategies.

***Maximilian von Eynatten, MD**

*Heidelberg University Hospital
Department of Medicine
INF 410
69120 Heidelberg
Germany
E-mail: maximilian.eynatten@med.uni-heidelberg.de

Jochen G. Schneider, MD
Per M. Humpert, MD
Joerg Kreuzer, MD
Helmut Kuecherer, MD
Hugo A. Katus, MD
Peter P. Nawroth, MD
Klaus A. Dugi, MD

doi:10.1016/j.jacc.2006.02.033

Please note: Drs. von Eynatten and Schneider contributed equally to this work.

REFERENCES

1. Pischon T, Girman CJ, Hotamisligil GS, et al. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730–37.
2. Schulze MB, Shai I, Rimm EB, et al. Adiponectin and future coronary heart disease events among men with type 2 diabetes. Diabetes 2005;54: 534–9.
3. Wolk R, Berger P, Lennon RJ, Brilakis ES, Somers VK. Body mass index: a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. Circulation 2003;108:2206–11.
4. Dugi KA, Brandauer K, Schmidt N, et al. Low hepatic lipase activity is a novel risk factor for coronary artery disease. Circulation 2001;104: 3057–62.
5. Yang WS, Tsou PL, Lee WJ, et al. Allele-specific differential expression of a common adiponectin gene polymorphism related to obesity. J Mol Med 2003;81:428–34.
6. Yamamoto Y, Hirose H, Miyashita K, et al. PPAR(gamma)2 gene Pro12Ala polymorphism might influence serum levels of an adipocyte-derived protein, adiponectin, in the Japanese population. Metabolism 2002;51:1407–9.
7. Qi L, Li T, Rimm E, et al. The +276 polymorphism of the APM1 gene, plasma adiponectin concentration, and cardiovascular risk in diabetic men. Diabetes 2005;54:1607–10.